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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	18

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/984,900	Anthony J.F. D'Apice et al.
Examiner	**Group Art Unit**
Shin-Lin Chen	1633

X Responsive to communication(s) filed on *Nov 8, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) *1-3, 46-51, and 67-73* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

X Claim(s) *1-3, 46-51, and 67-73* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* X None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendments filed 10-12-99 (Paper No. 15) and 11-8-99 (Paper No. 17) have been entered. Claim 67 has been amended. Claims 69-73 have been added. Claims 1-3, 46-51 and 67-73 are pending.

The polynucleotide sequences of SEQ ID No. 7 disclosed in Application No. 08/188,607, filed 1-27-94, and Application No. 08/378,617, filed 1-26-95, are 99.6% identical but not 100% identical to the polynucleotide sequence of SEQ ID No. 7 as disclosed in the present application. There are change of bases between the polynucleotide sequence of SEQ ID No. 7 of the present application and the polynucleotide sequence of SEQ ID No. 7 of either Application No. 08/188,607 or Application No. 08/378,617. Therefore, aplicant is not considered to be entitled to the earlier filing dates of Application No. 08/188,607 and 08/378,617 for SEQ ID No. 7. The effective filing date of the polynucleotide sequence of SEQ ID No. 7 of the present application would be the filing date of the present application, i.e. 12-4-97.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 70-73 recite the limitation "The porcine cell" in line 1 of each claim. There is insufficient antecedent basis for this limitation in the claim. No porcine cell has been mentioned in dependent claims 1 or 68.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 1-3 and 68 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Sandrin et al.,1998, US Patent No. 5,821,117 (A).

Claims 1-3 and 68 are directed to a nucleic acid molecule comprising SEQ ID No. 7, a sequence corresponding to SEQ ID No. 7 that is within the scope of the degeneracy of the genetic code, a nucleic acid sequences that hybridize to the sequence of SEQ ID No. 7 under high stringency condition, a host cell transformed with said nucleic acid and a porcine α-1,3,GT encoded by said nucleic acid.

Sandrin et al. teaches a porcine α-1,3 galactosyltransferase cDNA sequence (SEQ ID No. 2) which is 98.9% homologous (base 108-1335) to base 185-1412 of SEQ ID No. 7 of the present application and is capable of hybridizing to the sequence of SEQ ID No. 7 under high stringency

condition. Sandrin et al. also disclosed a λgt11 cDNA library expressing a porcine α-1,3,GT in a host cell for the isolation of the porcine α-1,3 GT cDNA (e.g. column 9, 10). Thus, claims 1-3 and 68 are anticipated by Sandrin et al..

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 46, 47, 67, 69 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sandrin et al.,1998, US Patent No. 5,821,117 (A).

Claims 46, 47, 67 and 70 are drawn to a DNA construct comprising a disrupted porcine α-1,3 galactosyltransferase (α-1,3, GT) gene, wherein the disruption is by the insertion of an exogenous sequence within exon 4, exon 7, exon 8, or exon 9 of the porcine α-1,3 GT gene and the disruption prevents expression of a functional α-1,3, GT. Claims 67, 69 and 70 are directed to a porcine cell comprising at least one inactivated α-1,3, GT gene, wherein the disruption is by the insertion of an exogenous sequence within exon 4, exon 7, exon 8, or exon 9 of the porcine α-1,3 GT gene and the disruption prevents expression of a functional α-1,3, GT.

Sandrin teaches a porcine α-1,3 galactosyltransferase cDNA sequence (SEQ ID No.2) which is 98.9% homologous (base 108-1335) to base 185-1412 of SEQ ID No.7 of the present application and discloses a λgt11 cDNA library expressing porcine α-1,3 GT in a host cell for the isolation of the porcine α-1,3,GT cDNA (e.g. column 15-18). Sandrin teaches a method of inhibiting xenotransplant rejection in an animal patient by introducing mutants of nucleotide sequences in a vector, such as plasmid or viral vector encoding α-1,3 GT, into embryonic stem cells via homologous recombination for the inactivation of wild type α-1,3 GT genes, wherein the mutant α-1,3 GT nucleotide sequences include nucleotide deletions, insertions, substitutions and additions to wild type α-1,3 GT gene such that the resultant mutant does not encode functional galactosyl transferase (e.g. column 1, 3, 9, 10).

Sandrin does not teach using an exogenous sequence to introduce a disruption within exon 4, exon 7, exon 8, or exon 9 of the porcine α-1,3 GT gene. The exogenous sequence used

to disrupt the porcine α-1,3 GT gene may be different from the insertions or additions of the nucleotide sequences of the wild type α-1,3 GT gene such that the resultant mutant α-1,3 GT gene does not encode functional galactosyl transferase. It would have been obvious for one of ordinary skill to use exogenous sequences as recited in the present application or inserting nucleotide sequences into porcine α-1,3 GT gene as taught by Sandrin because they both are for the purpose of generating a disrupted porcine -1,3 GT gene and a transgenic pig having non-functional α-1,3 GT genomic sequences, wherein the tissue derived from such transgenic pig sould be utilized in xenotransplantation into human patients and avoid hyperacute rejection. Furthermore, it would be obvious for one of ordinary skill in the art to introduce an exogenous sequence within exon 4, 7, 8, or exon 9 of a porcine α-1,3,GT gene to interrupt α-1,3 GT gene which results in non-functional α-1,3,GT, such that a transgenic pig having non-functional α-1,3 GT genomic sequences could be obtained and the tissue derived from such transgenic pig could be utilized in xenotransplantation into human patients and avoid hyperacute rejection response.

Thus, it would have been obvious to one of ordinary skill in the art at the time of the invention to introduce an exogenous sequence within exon 4, exon 7, exon 8, or exon 9 of a porcine α-1,3,GT gene to generate a DNA construct comprising a disrupted porcine α-1,3 GT gene, and a porcine cell comprising said DNA construct.

One having ordinary skill would have been motivated to do so in order to obtain a porcine cell comprising a disrupted porcine α-1,3 GT gene, or a porcine organ lacking or having reduced

α−1, 3 GT activity so as to reduce or eliminate hyperacute rejection response in humans during xenotransplantation as taught by Sandrin.

7. Claims 46-51, 67 and 69-73 are rejected and claims 69-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sandrin et al., US Patent 5,821,117 (A) and Galili, 1993 (U) in view of Hodges et al., 1996, US Patent No. 5,527,695 (B) and the effective filing date for the sequence of SEQ ID NO. 7 of the present application as set forth above.

Claims 46-51 and 67 are drawn to a DNA construct comprising a disrupted porcine α-1,3 galactosyltransferase (α-1,3, GT) gene, wherein the disruption is accomplished by the insertion of an exogenous sequence such as a neo^R gene or a hyg^R gene within exon 4, exon 7, exon 8, or exon 9 of the porcine α-1,3 GT gene, and wherein stop codons have been inserted 3' to the selectable marker. Claim 50 specifies the exogenous sequence is flanked at its 5' and 3' ends by FLP recombinase target site (FRT) DNA elements. Claim 51 specifies a method for generating a porcine cell comprising at least one inactivated α-1,3 galactosyltransferase by introducing the DNA construct set forth above into porcine cells such that homologous recombination occurs between chromosome sequence and DNA construct. Claim 67 and 69-73 are directed to a porcine cell comprising at least one inactivated α-1,3, GT gene, wherein the disruption is by the insertion of an exogenous sequence into said gene. Claim 70 specifies the disruption is within exon 4, exon 7, exon 8, or exon 9 of the porcine α-1,3 GT gene. Claims 71 and 72 specify the

exogenous sequence is a selectable marker such as neo^R gene or hyg^R gene. Claim 73 specifies the exogenous sequence is flanked at its 5' and 3' ends by FRT DNA elements;

Sandrin teaches a porcine α-1,3 galactosyltransferase cDNA sequence (SEQ ID No.2) which is 98.9% homologous (base 108-1335) to base 185-1412 of SEQ ID No.7 of the present application and discloses a λgt11 cDNA library expressing porcine α-1,3 GT in a host cell for the isolation of the porcine α-1,3,GT cDNA (e.g. column 15-18). Sandrin discusses the hyperacute rejection response associated with xenotransplantation, particularly in the context of pig tissue as associated with antibodies reactive with galactose in an α-1,3 linkage with galactose. Sandrin teaches a method of inhibiting xenotransplant rejection in an animal patient by introducing mutants of nucleotide sequences in a vector such as plasmid, viral vector encoding α-1,3 GT, into embryonic stem cells via homologous recombination for the inactivation of wild type α-1,3 GT genes, wherein the mutant α-1,3 GT nucleotide sequences include nucleotide deletions, insertions, substitutions and additions to a wild type α-1,3 GT gene such that the resultant mutant does not encode functional galactosyl transferase. Sandrin also teaches the vectors encoding α-1,3 GT may include restriction sites for the insertion of additional genes and/or selection markers, as well as elements necessary for the propagation and maintenance of vectors within cells (e.g. column 1, 3, 9, 10).

Galili discusses that the immunological barrier by anti-Gal interacting with α-galactosyl epitopes on the discordant graft cells might be difficult to overcome by means of

immunosuppression, and suggests the use of xenografts devoid of α-galactosyl epitopes obtained from nonprimate donors which are genetically engineered to lack α-1,3 GT activity by gene knockout technology or by the production of transgenic animals with anti-sense DNA to the α-1,3 GT gene (e.g. p. 482).

Hodges teaches generating a DNA construct containing a FRT site and a selectable marker gene neo for a specific integration of a gene into the genome of an eukaryotic cell via homologous recombination (e.g. column 21, 22).

Sandrin et al. and Galili do not teach introducing the exogenous sequence within exon 4, 7, 8, or exon 9 of the porcine α-1,3,GT gene, or using the exogenous sequence such as neo^R gene or hyg^R gene flanked at its 5' and 3' ends by FRT DNA elements.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a selectable marker gene such as neo and a FRT site for homologous recombination as taught by Hodges for generating a DNA construct comprising a disrupted porcine α-1,3, GT gene and a porcine cell comprising said disrupted porcine α-1,3, GT gene as taught by Sandrin. It would be obvious for one of ordinary skill in the art to introduce an exogenous sequence within exon 4, 7, 8, or exon 9 of a porcine α-1,3,GT gene to interrupt α-1,3 GT gene, as Sandrin teaches, for generating mutant α-1,3 GT nucleotide sequences via nucleotide deletions, insertions, substitutions and additions to a wild type α-1,3 GT gene, such that a transgenic pig having non-functional α-1,3 GT genomic sequences would have been obtained. The tissue

derived from such transgenic pig would have been useful in xenotransplantation into human patients so as to avoid hyperacute rejection response.

One having ordinary skill in the art would have been motivated to have introduced a specific disruption to a porcine α-1,3, GT gene via homologous recombination of a FRT site and to select the transformed cells containing a disrupted porcine α-1,3, GT gene with a selectable marker gene such as neo, because generation of a porcine cell comprising a disrupted porcine α-1,3, GT gene would have allowed for the development of a porcine organ lacking α-1,3 GT activity. Such would have provided the benefit of preventing xenotransplant rejection in an animal patient. Such would have been expected because it was known in the prior art that the hyperacute rejetion response of xenotransplantation in a human patient would have been avoided when using a porcine organ lacking α-1,3 GT activity as taught by Sandrin and Galili.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.